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NUTRITION REVIEWS

VOL. 15 JULY 1957 No. 7

OVERNUTRITION FOR THE CHILD: BLESSING OR CURSE?

Throughout the past century nutritional science has been preoccupied with the deficiency concept of disease. In the field of child health this orientation has been a most fruitful one, for the growing organism's needs are great and deficiency states quick to develop. The recent wave of interest in the malignant malnutrition syndromes (Kwashiorkor) has served once again to emphasize the tragic nutritional handicap which still confronts so many children in underdeveloped areas today. No one can deny the seriousness of this situation. Yet we should remember that undernutrition is no longer a problem of major importance in certain parts of the world. Despite the untiring efforts of nutritionists in uncovering dietary inadequacies in our population, it has become increasingly apparent that in those regions of the United States where good medical care is enjoyed, clinically recognizable deficiency states are rather uncommon among children. Many medical students graduate without having seen a case of rickets or scurvy, and instances of florid malnutrition are rarely seen in the absence of provocative illness.

Certain nutritional excesses are today a matter of great concern with regard to adults since there is much evidence to indicate that health and longevity are thereby impaired. The case against overfeeding, so forcibly portrayed in McCay's classic experiments, has been documented for many species, including man (Silberberg and Silberberg, *Physiol. Rev.* **35,** *347 (1955)*). Certainly the idea that dietary excesses can be harmful is not a new one. Listen to Spenser as he describes Duessa's second counsellour:

> "Full of diseases was his carcas blew,
> Which by misdiet daily greater grew:
> Such one was Gluttony . . ."

We can only guess whether the poet by intention placed him between Idlenesse and Lecherie in the ranks of "this ungodly tire"! In the modern setting there is a wealth of evidence to indicate that adult obesity is associated with increased mortality, and many physicians classify overfeeding as a form of malnutrition.

There are subtle indications that overnutrition in infants and children may be a factor to be reckoned with. Certainly childhood obesity is in many ways more of a therapeutic problem for the modern pediatrician than is malnutrition. Recent surveys tell us that ten per cent of the child population can be classed as definitely overweight (Johnson *et al., Am. J. Clin. Nutrition* **4,** *231 (1956)*).

Turning to more specific dietary elements, interest in the present subject has been stimulated by the recently described syndrome of "hypercalcemia in infancy with failure to thrive." This fascinating yet poorly understood condition is characterized by a multitude of signs and symptoms, including hypercalcemia, azotemia, albuminuria, failure to grow and develop, and occasionally by more severe manifestations such as osteosclerosis, hypertension, and renal failure. A number of possible causes have been suggested (*Nutrition Reviews* **14,** *338 (1955)*), yet it is the author's opinion that overdosage of vitamin D cannot as yet be excluded from the list. Why is the condition so common in Great Britain in the face of a complete lack of reported cases in this country? The resemblance of these cases in certain respects to known instances of vitamin D intoxication, together with the earlier observations of Jeans on the possible deleterious effects of a daily intake of only 1800 units, prompts one to inquire into possible differences between British

and American feeding habits. British cod liver oil has approximately twice as much vitamin D as the U.S.P. preparation; precooked infant cereals are fortified with vitamin D whereas analogous products made in this country are not; and their proprietary milk products contain about three and one-half times as much vitamin D as those used in this country. An *ad hoc* committee of the British Paediatric Association concluded that the daily intake could be as high as 4,000 units, or *ten times* the minimal requirement (*Brit. Med. J.* **2,** *149* (*1956*)).

It is of the greatest interest that the increases in degree of fortification of British foods were effected just a few years prior to the first reports of this syndrome. Analyses of the foods have revealed a higher content than stated on the label, presumably to allow for deterioration during storage. To the associative implications of such a nice temporal relationship could be added the catalytic effect of the National Health Service Act, which among other things decreed that cod liver oil should be distributed free of charge!

That large doses of vitamin A can result in toxic symptoms is well known—hyperostosis, hepatomegaly, painful subcutaneous swellings, and partial loss of hair have been described in children. Interestingly enough, there are recent reports of toxicity from the use of excessive amounts of vitamin K in young infants (*see* Meyer and Angus, *Arch. Dis. Childhood* **31,** *212* (*1956*)). Doses of 10 mg. or more have been associated, particularly in prematurely born infants, with elevated serum bilirubin levels, hemolytic anemia, and an increased incidence of kernicterus.

As far as the more general aspects of nutritional excess are concerned, the older clinicians were convinced that the fat infant tolerated gastrointestinal infections poorly. Weight reduction often has a salutary effect on infantile eczema. And in the case of the newborn there seems to be an optimal birth weight at which neonatal mortality is lowest, with appreciably greater mortality rates for the big baby as well as for the prematurely born (Baumgartner *et al.*, *Pediatrics* **6,** *329* (*1950*)). The human organism is not unique in this latter respect, for a plot of hatchability of hen's eggs against egg weight exhibits a well-defined maximum (Needham, *Biochemistry and Morphogenesis*, *1950*).

Modern mothers are constantly being reminded of the concept that bigger babies are better babies, which is but one manifestation of a frame of mind which pervades our culture. One nationally advertised polyvitamin preparation boasts that it provides among other excesses *four times* the daily requirement of vitamin D. The commercial advocates of lysine supplementation for infant diets are busily engaged in orienting the physician's viewpoint towards their product. Pediatricians vie in the art of earlier and earlier introduction of solid foods.

The infant and child of today is bigger, and grows faster than his counterpart of a half-century ago. The old maxim that a baby doubles his birth weight by five months of age is fast losing ground among clinicians since many accomplish this by 3 to 4 months. Meredith has concluded that the one year old infant is seven per cent taller than his 19th Century counterpart, though the difference in length at birth is only one per cent. Nine to fourteen year old boys are six to eight per cent taller and twelve to fifteen per cent heavier than formerly. (*Physical Growth from Birth to Two Years*, (*1943*); *Am. J. Dis. Child.* **62,** *909* (*1941*)). Menarchal age is on the average lower, as is the age of the adolescent growth spurt in both boys and girls. Morant has shown that the maximum height of the British male is now reached at age 21½ years rather than 26 years as in 1880, though contrary to popular belief the mean maximum height has not changed (*Proc. Roy. Soc. B* **137,** *443* (*1950*)).

How is one to account for this trend? Is it

the result of the lessening of the frequency of serious disease on the one hand, of better nutrition on the other, or perhaps both operating together? Or is it merely a consequence of the phenomenon of "hybrid vigor?" There are of course many factors which enter into the determination of growth performance—race, sex, parental size, socio-economic status, etc., and it would be unwise to become dogmatic as to the causes of the observed secular changes in growth and maturation.

The observations which have been made on obese children would tend to indicate that changes in nutritive status have played a role here. On the average, the obese child is taller than normal and exhibits advanced skeletal maturation; in girls menarchal age is lower. Recent studies (Wolff, *Quart J. Med.* **24,** *109* (*1955*)) offer definitive support for the contention that the observed advancement in height and maturation is a consequence of increased food intake, rather than some hypothetical endocrine factor.

Should we be concerned about the well documented secular changes in children's growth rates? Meredith sidesteps the question neatly by stating that evaluation "will require more extensive study than has been necessary for the discovery of these changes. . . . It is possible that (this trend) may be found desirable, undesirable, or unrelated to the criteria." There is no large body of evidence, as there is for the adult, to indicate that childhood obesity is detrimental to physical health, and at present one can only keep in mind the more fragmentary bits referred to earlier while not forgetting the conclusions drawn from animal feeding experiments.

At the risk of exposing oneself to the teleological critics, it is pertinent to inquire at this point into the matter of breast versus artificial feeding for infants. Why does breast milk contain significantly smaller amounts of many dietary essentials than does cow's milk? Why does the average breast fed infant receive for the most part less of these essentials than the National Research Council recommendations call for? The phenomenon of "supermineralization," by which is meant the greater retention of minerals and nitrogen by the cow's milk fed baby, has intrigued the metabolic balance experts for half a century. Neonatal tetany (hypocalcemic) occurs almost exclusively in the artificially fed baby, as a consequence of the high phosphorus content of cow's milk. The infantile hypercalcemic syndrome, referred to earlier, almost never occurs in breast fed babies, thus raising the question of a possible effect from the high calcium content of cow's milk. The author's clinical impression is that the breast fed baby is not as heavy as his artificially fed counterpart, and there is some statistical evidence from recent Iowa studies to support this. (Contrast Frost and Jackson, *J. Pediat.* **39,** *585* (*1951*) with Paiva, *Pediat.* **11,** *38* (*1953*)). In general the reverse situation obtained some 75 years ago. And here is where the teleologist can make a telling point: the growth curve drawn by the elder Camerer (circa 1870) for the breast fed baby can be superimposed upon the one based on the most recent observations of the Iowa group! Admittedly, the interpretation of such comparisons is most difficult, yet the mere suggestion that weight gains in the nursling have remained the same while the bottle fed baby has come from behind, not just to equal but actually to surpass him, should raise questions as to the desirability of this trend.

What is optimum nutrition? Until a better definition is forthcoming, we cannot categorically conclude that maximum growth is the optimum. Were yesterday's children undernourished, or are today's children overweight and overdeveloped in comparison to the normal 19th Century specimen, and destined, as were McCay's rats, for an earlier death? We must continue to remind ourselves that human growth data are empirical: there is no satisfactory mathematical model for the curve of human growth, no

theoretical basis for its shape, which (except for primates) is unique among mammals.

The long life span of man makes longitudinal studies difficult, and advances in medical practice renders their interpretation hazardous, since the risk of ill health will change during the observational period. But sufficient data are at hand to indicate that the slope of the human growth curve is not a biologic invariant. We are now in an era of child care in which many former deterrents to good health have largely disappeared; an era which has witnessed significant advances in food technology, widespread use of promotional advertising, and the general availability of highly potent dietary supplements. Thus, overnutrition is easier to achieve. Consequently, the definition of optimal nutrition constitutes more of a challenge, and it is not unlikely that future pediatric practice will be to some extent concerned with the stress of overnutrition.

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PHYSIOLOGIC RESULTS OF BREAKFAST HABITS

The idea that an adequate breakfast is important is not new, but it has been only recently that well-controlled experiments have been carried out to support this view. In order to gain information concerning the role of breakfast in the diet regimen, numerous experiments have been done during the past six years to show the effects of altering breakfast habits on efficiency in the late morning hours, as indicated by the effects of various breakfast plans on physiologic responses.

The experiments reported by W. W. Tuttle and his collaborators, who have done much in the past ten years to fill the existing need for well-controlled work on tl s subject, involve both male and female subjects, and include an age range of 12 to 82 years. The investigators arranged a plan whereby controlled diets, designed and supervised by the dietitians, were served in a hospital dining room. They were particularly interested in the effects of different breakfasts on physiological responses during the late morning hours. Their main tests involved simple and choice reaction time, neuromuscular tremor magnitude, maximum grip strength, grip strength endurance, maximum work rate, maximum work output, and oxygen required to perform a specific amount of work.

An experiment on the effects of the omission of breakfast on efficiency in the late morning hours was reported by Tuttle, M. Wilson, and K. Daum (*J. Applied Physiol.* **1,** *545* (*1945*)). It involved six normal women, of ages 22 to 27 years. It was found that the omission of breakfast resulted in a decrease in maximum work output, and an increase in simple and choice reaction time, as well as in neuromuscular tremor magnitude. In a similar experiment reported by Tuttle, Daum, L. Myers, and C. Martin (*J. Am. Dietet. Assn.* **26,** *332* (*1950*)), in which the subjects were 11 men of ages 21 to 28 years, the data showed that the omission of breakfast resulted in an increase in neuromuscular tremor magnitude and choice reaction time, and a decrease in maximum work output.

Tuttle, Daum, C. J. Imig, B. Randall, and M. T. Schumacher (*J. Am. Dietet. Assn.* **28,** *117* (*1952*)) reported an experiment dealing with the physiologic effects of the omission of breakfast on male subjects of 60 to 82 years of age. They found as a result of omitting breakfast, that in one-half of the subjects there was a significant increase in neuromuscular tremor magnitude, a decrease in maximum grip strength and grip strength endurance, and an increase in the amount of oxygen required to perform a specified amount of work.

The last experiment in this series was reported by Tuttle, Daum, R. Larsen, J. Salzano and L. Roloff (*J. Am. Dietet. Assn.* **30,** *674 (1954)*). The study involved seven school boys of 12 to 14 years of age. The data showed that the omission of breakfast not only resulted in a significant decrease in maximum work rate and maximum work output in the late morning hours, but also exerted a detrimental effect on the attitudes and scholastic attainments of the school boys. On the other hand, there was no change in reaction time, tremor, grip strength, or endurance. These investigators extended this experiment to include 18 school boys who ate their meals at home, the only restrictions being the omission of breakfast at stated intervals. The results paralleled those found when the total daily diet was controlled.

The data presented relative to the effects of the omission of breakfast indicated that the result is a decrease in efficiency in the late morning hours.

In conjunction with the experiments involving the omission of the morning meal, attention was given to the effects of the size and content of the breakfast on efficiency in the late morning hours, as indicated by the physiologic responses of the subjects. Tuttle, Wilson, and Daum (*loc. cit.*) reported the effect of coffee alone, as compared with that of a light and heavy breakfast, using as subjects a group of six women of ages 20 to 37 years. They found that when coffee was substituted for a heavy breakfast, there was a decrease in maximum work output, and an increase in neuromuscular tremor magnitude and choice reaction time. When a light breakfast was eaten instead of coffee alone, maximum work output and choice reaction time improved, and neuromuscular tremor magnitude decreased.

A group of women at ages 18 to 25 years were employed by Daum, Tuttle, Martin, and Myers (*J. Am. Dietet. Assn.* **26,** *503 (1950)*) to show the effects of various types of breakfasts on physiologic response in the late morning hours. They established no significant differences between physiologic responses studied following a light breakfast (300 Calories) and those following a heavy breakfast (1000 Calories). However, a 600 Calorie breakfast resulted in significantly better responses than those following no breakfast.

The effects of breakfasts of different sizes and contents were also investigated by Tuttle, Daum, Imig, Martin and R. Kisgen (*J. Am. Dietet Assn.* **27,** *190 (1951)*). Data collected from ten male subjects between the ages of 20 and 35 years, showed no significant differences in physiologic responses studied 3 to 5 hours following the regular consumption of a 750 Calorie cereal and milk breakfast and a 750 Calorie bacon, egg, and milk breakfast. The same relative results followed when both breakfasts were increased to 1200 Calories. However, when the physiologic responses following a 750 Calorie breakfast were compared with those following a 1200 Calorie breakfast, it was found that 75 per cent of the subjects did significantly more work in the late morning hours following the smaller breakfast.

In another experiment along this line, Tuttle, Daum, H. Roberts, and Randall (*J. Am. Dietet. Assn.* **29,** *35 (1953)*) observed the effects of the size and content of breakfast on a group of seven men, of ages 60 to 82 years. It was concluded that the content of the breakfasts, which consisted of ordinary breakfast items, made no difference as far as the maintenance of efficiency in the late morning hours was concerned. It was found, however, that a breakfast providing one-fourth the daily caloric requirement and protein allowance was superior to a heavy breakfast in maintaining efficiency. Daum, Tuttle, Larsen, Roloff and Salzano (*J. Am. Dietet. Assn.* **31,** 359 (1955)) investigated the effects of different breakfasts on the physiologic responses of eight school boys, between the ages of 12 and 14 years. The data showed that no significant differences in physiologic responses in the

late morning hours resulted from two breakfasts which were essentially similar, with one built around cereal and milk and the other based upon bacon, eggs, and milk.

The data presented by the various investigators seem to show that a breakfast containing one-fourth the daily caloric requirement and protein allowance is to be preferred to a heavy breakfast.

The examination of their data shows that the results quoted above are average results, and as such appear to be significant. However, in most of the experiments one or more of the tests either did not show any change or went in the opposite direction. Also, in some experiments the performance of one or more subjects appeared to be improved, in several tests, by omitting breakfast. Hence, we must conclude not only that the nutritional make-up of breakfast is important, but also that there is a considerable degree of variation between individuals in their physiologic and, no doubt, emotional, response to breakfast.

CALCIUM METABOLISM IN HUMANS

Prior to the advent of radioisotopes in biological research, factors governing the metabolism of calcium were poorly understood because it was impossible to distinguish endogenous from exogenous calcium in the serum, urine, skeleton and feces. Consequently, the availability of Ca^{45} for use in experimental studies has provided the stimulus for reinvestigation of many problems of calcium metabolism.

F. Bronner and R. S. Harris (*Ann. N. Y. Acad. Sci.* **64,** *314* (*1956*)) have focused attention on calcium metabolism in human subjects. An initial study was carried out on boys aged 11 to 16 years and adults aged 21 and 22 years. All were institutionalized for mental inadequacy but were otherwise normal and in good health. Ca^{45} was administered by means of two methods: (1) Following an overnight fast of 12 hours, Ca^{45} was mixed in 60 ml. of milk and served with a standard breakfast of rolled oats or farina; (2) In some cases the isotope was given intravenously 30 minutes after the standard breakfast. Serum, urine and feces were assayed for total calcium by the method of K. B. Salomon, W. Gabrio and G. D. Smith, (*Arch. Biochem.* **11,** *433* (*1946*)), and for Ca^{45} by counting Ca oxalate samples containing 4.0 mg. calcium.

It was found that when Ca^{45} was injected intravenously, more than four fifths of the isotope disappeared from the circulation within five minutes. After the initial adjustment, and even two months after the injection, the specific activity of the serum did not taper off. This observation places emphasis on the large role played by the skeleton in calcium metabolism. The authors estimate that up to 100 times more exchangeable calcium is present in the skeleton than in the serum.

The injected Ca^{45} disappeared from the blood of the boys five to six times faster than from the blood of the young adults. Since the size of the various calcium compartments was not analyzed it is not known whether the adults differed from the boys in the size of calcium compartments, in equilibrium rate, or both. However, data on urinary and fecal output suggest a smaller retention in the skeleton of the young adult.

It was found that under conditions of the standard breakfast, nearly half of the Ca^{45} eaten was recovered from the feces in three days. However, when the Ca^{45} was given intravenously, less than 5 per cent of it was detected in the feces during a similar period. This indicates that only an inappreciable fraction of absorbed calcium is re-excreted in the feces during the first days following absorption, and that Ca^{45} appearing in the feces after a test meal is largely the result of a failure to absorb all of the calcium. Ex-

periments on two groups of boys given the same test breakfast, but different amounts of Ca^{45}, showed that proportionately less calcium was absorbed as calcium intake increased. The authors are of the opinion that the per cent of calcium absorbed is an exponential function of the calcium intake.

Some controversy exists in the literature regarding the role of the feces in calcium homeostasis. Evidently there are species differences in the way endogenous calcium is partitioned between the feces and the urine, but the present studies leave little doubt that human beings, as well as all animals studied, excrete some endogenous calcium via the feces. The major route of excretion in the human, however, was found to be via the urine.

In an effort to determine which of the metabolic processes is rate-limiting for retention of calcium, the authors considered absorption, transport, bone salt formation, bone salt resorption, and excretion.

The speed with which injected Ca^{45} left the bloodstream indicated that calcium transport in the blood could in no way limit the possibilities of calcium retention. Their conclusion from the foregoing data was that neither calcium absorption, excretion, nor transport, was the slowest process in the chain of events related to calcium metabolism. Thus, either bone salt formation or bone salt resorption is implicated.

If it is assumed that, following injection of Ca^{45}, the specific activity of the exchangeable calcium in the skeleton very rapidly equilibrates with that of the serum, then the quantity of exchangeable Ca^{45} in the skeleton at any time equals the specific activity of the blood calcium multiplied by the quantity of exchangeable calcium, in the skeleton. The quantity of accreted calcium for any period will equal the mean specific activity for the period multiplied by the accretion rate and the time elapsed.

When this relationship was applied to human subjects it was found that bone salt accreted at the rate of approximately 2 g. calcium per day in the case of the boys and about 75 g. calcium per day in the case of young adults. Bone salt resorption in the boys was at a rate of no less than 1 g. of calcium per day. In the adults it was correspondingly lower.

The authors state that it is impossible to determine from the above data whether bone salt accretion or resorption is the slowest process of calcium metabolism. They suggest that both may be limiting. A. Carlson (*Acta Pharmacol. Toxicol.* **7,** *Suppl. 1* (*1951*)) has suggested that resorption, rather than accretion, is the homeostatic process. If this were true, decreased calcium intake would result in proportionately increased resorption of bone marrow, and according to the authors, bone salt accretion would be the limiting process.

THE ANEMIA OF KWASHIORKOR

Kwashiokor is a deficiency disease seen mostly among young children in the tropics. The clinical signs include growth failure, edema, lowered plasma albumin, impaired gastro-intestinal function, dermatosis, fatty liver, and anemia. It is generally considered that the disease is related to an inadequate intake of animal protein (*Nutrition Reviews* **8,** *161* (*1950*); **13,** *1* (*1955*); **13,** *67* (*1955*)).

The anemia of kwashiorkor does not respond to liver extract, folic acid, or to hog's stomach preparations (H. C. Trowell, *Tr. Roy. Soc. Trop. Med. Hyg.* **42,** *417* (*1949*)). It was pointed out by H. C. Trowell (*Arch. Dis. Childhood* **20,** *110* (*1945*)) that the high incidence of parasitic infestations among children with kwashiorkor complicates the peripheral blood picture. In this connection, H. Lehmann (*Lancet* **I,** *90* (*1949*)), in a study of 44 cases of kwashiorkor, reported

that in all instances there was evidence of peripheral blood loss due to hookworm and malaria. The slight macrocytosis was considered to reflect bone marrow hyperactivity in an effort to compensate for the loss of blood due to excessive hemolysis.

In support of the role of parasitic infestation in producing the anemia of kwashiorkor, Altmann and J. F. Murray (*South African J. Med. Sci.* **13,** *91 (1948)*) found that in Johannesburg the incidence of parasitic infestation was quite low and that the anemia of kwashiorkor in this region was mild and usually normocytic. Treatment with milk led to a hematologic response, and it was concluded that the anemia was due to protein deficiency.

A detailed study of the bone marrow from seven children suffering from kwashiorkor has been presented by K. Lien-Keng (*Blood* **12,** *171 (1957)*). These children were patients at the Pediatric Clinic of the University of Indonesia. The incidence of parasitic infestation was not stated, but the usual clinical signs of kwashiorkor were observed. The children were all anemic to a moderate degree.

The bone marrow studies revealed a condition of erythroblastopenia, a reduction in the number of cells which differentiate into erythrocytes. This finding indicates that the anemia in these cases was due to bone marrow insufficiency, probably related to dietary protein deficiency. It is well known that protein malnutrition in experimental animals may lead to anemia.

It thus appears that the anemia of kwashiorkor is relatively mild, normocytic, and due to bone marrow insufficiency. The presence of parasitic infestation complicates the condition because of the greatly increased rate of blood loss, which increases the severity of the anemia and usually results in macrocytosis.

THE PREDICTION OF ADULT BODY MEASUREMENTS

There is very little information available concerning the relationships between growth during infancy and adult shape and size. Such data might be expected to give information permitting some degree of interpretation concerning the relative roles of nutrition and genetic growth factors. J. M. Tanner and co-workers (*Arch. Dis. Childhood* **31,** *372 (1956)*) have seized upon a rather unusual opportunity to correlate anthropometric data obtained during the first five years of life with similar observations made on the subjects when they were between the ages of 25 and 30 years.

Between 1923 and 1927 a series of newborn babies was studied by A. Low and a report was published posthumously (*Growth of Children, Aberdeen University Press 1952, p. 64*). Low's data consisted of measurements on 65 boys and 59 girls. Twenty-one physical measurements were taken on each child at each birthday until the age of five years.

Tanner and co-workers were able to find, and remeasure, exactly 65 per cent of the original group of both men and women after a period of 20 to 25 years, using the same techniques as were used by Professor Low. In the present paper they are concerned with the prediction of adult measurements from childhood ones, and give the correlations of the data on supine length, weight, head length and breadth, shoulder and hip width, and length of the lower arm and foot. Intercorrelations between measurements each year were given for each dimension and also the cumulative percentages of the adult variance were explained by multiple regressions using all measurements up to 0, 1, 2, 3, 4, and 5 years, respectively. The use of the Elliott Mark I electronic computer greatly facilitated the calculations involved.

The original sample constituted a pure longitudinal series in that every child was present at every age. The correlations made between the data obtained on the third day

of life and that obtained at years one through five were considerably lower than the intercorrelations between the later figures. For example, the lower arm length measurements at birth correlated very poorly (0.15 to 0.35) with those made at years one through five whereas the correlations between the one-year-old and subsequent measurements were over 0.65.

The poor correlation between birth measurements and those made during infancy and early childhood were interpreted by Tanner and co-workers as being due to several possibilities. They rejected the possibility that a larger measuring error was present at birth than subsequently. Maternal malnutrition during pregnancy was considered unlikely, since similar low correlations between birth and subsequent measurements had been noted in other studies in which the maternal diet was thought to have been nearly optimal (K. Simmons, *Monographs of the Society for Research on Child Development* **9,** *No. 1 (1944)*; N. Bailey and F. C. Davis, *Biometrika* **27,** *26 (1935)*).

J. Thomson (*Arch. Dis. Childhood* **31,** *382 (1956)*) has recently made almost 5,000 sets of observations on Edinburgh infants during the first year of life, limited to legitimate, singleton, first pregnancy infants with birth weights between 5½ and 9½ pounds. In this recent study there was also a significant negative correlation between measurements at two weeks and the subsequent increment, suggesting a strong tendency for infants who were small at birth to grow more rapidly than infants who were larger.

Consequently, Tanner and co-workers suggest that, in man, the inborn growth rate of the fetus is modified during the last two months or so of pregnancy by maternal factors which are quite distinct from the maternal genes influencing the child's ultimate size, and that these factors affect not only the rate of prenatal growth but also the gestation time. Such factors appear to be both systemic and uterine and serve to hold back in growth, and to expel early, the genetically large child who happens to be developing in a small sized mother. Such factors operating toward the end of pregnancy presumably produce only temporary alterations in the growth pattern, and the suppression of growth in the genetically large infant is followed during the first six months of life by a compensatory rapid gain in weight.

The correlation coefficient of the measurements at birth and at subsequent birthdays through age five with adult measurements are presented graphically. In general, there is a steep rise in adult predictability from birth to two years.

After this age the predictability is not greatly increased. Predictability is greatest for supine length, with a correlation coefficient at four years of 0.81. The data for weight do show a rise but a very small one, going only from 0.40 to 0.53. The data for shoulder width (biacromial) and hip width (bitrochanteric) reach a peak at two years and then decrease to correlations almost as low as those present at birth. This diminution in predictability of adult size at the ages of four and five years would suggest alterations in growth similar to those occurring during adolescence. However, such alterations in growth at this age are not generally recognized. When data at all previous ages are included in the calculations, they contribute little or nothing to the prediction of adult measurements.

Predictions for the male were lower correlation than for the female. The explanation for this is very likely that the adolescent spurt in males is of greater magnitude, and certainly of greater variability, than in females. Despite these considerations, it was pointed out that for supine length the predictabilities for both male and female were almost identical. Regressions of adult supine length on length at age three are given for both men and women with standard errors of estimate of 39 and 36 mm. Despite the fact that the great majority of head growth occurs by five years of age, the prediction of adult head size was relatively less accurate

than that for supine length. The reason for poor predictability of body breadths was not at all clear. The possibility that breadth may be more affected by environmental circumstances than is length was seriously considered.

The present study, which is the first of a series of papers to appear concerning this group of individuals, demonstrates at least one technique for estimating the consistency of linear growth, and points out quite distinctly some of the gaps in our knowledge.

PROTEOLYTIC ACTIVITY OF THE PANCREAS

During studies on a group of patients considered to have fibrocystic disease of the pancreas in the light of both clinical and laboratory evidence, J. G. Bate and U. James (*Arch. Dis. Childhood* **31,** *506 (1956)*) observed both clinical recovery and subsequent normal levels of trypsin in the duodenal juice. Ten children diagnosed as having chronic gastro-enteritis with failure to gain weight and abnormally offensive and bulky stools, sometimes with repeated respiratory infections, were found to have low concentrations of trypsin in the duodenal juice.

These infants and children were treated with pancreatin and reinvestigated after periods varying from two months to two years, in which time they had made a clinical recovery which was maintained, and trypsin was present in the duodenal juice in normal concentrations. The diagnosis of fibrocystic disease was no longer tenable. The absorption curves of plasma amino acid nitrogen, following a test dose of gelatin, were flat or showed a minimal rise initially in three of these patients; after clinical recovery normal amino acid absorption curves were found, indicating normal gelatin digestion.

In a second group of nine infants suffering from acute gastro-enteritis with losses in body weight between 7 and 25 per cent, duodenal trypsin activity was within normal limits. These children did show low, or flat, absorption curves following the test dose of gelatin. Following recovery the digestion of the gelatin test meal was normal, as interpreted by the amino acid absorption curves.

Eight malnourished children were studied similarly. They were grossly underweight as a result of underfeeding due either to mismanagement or neglect. Duodenal trypsin was diminished in one of the four children so examined. The amino acid absorption curves were low, but they returned to normal following clinical improvement on full feeding regimens.

In discussing their findings, Bate and James point out that the proteolytic activity of the pancreas is depressed in chronic and acute gastro-enteritis, and in malnutrition in infancy. This pancreatic function returns to normal when clinical recovery ensues. Such pancreatic depression would be expected in gastro-enteritis when the weight loss exceeds 7 per cent of the body weight or when feeding is restricted for seven days or longer. They felt that oral pancreatin might be beneficial in speeding up recovery after gastro-enteritis when the weight loss exceeds 18 per cent of the body weight. Depression of the amino acid absorption curves in the presence of apparently adequate levels of tryptic activity was interpreted by them to suggest that amino acid absorption curves are a more sensitive measurement of the proteolytic activity of the pancreas than the estimation of duodenal trypsin. However, amino acid absorption curves following a test dose of amino acid rather than gelatin, in order to detect a possible defect in amino acid absorption which might exist in the absence of a defect in gelatin digestion were not performed.

The recognition of instances of diminished,

or absent, duodenal trypsin in patients who apparently did not have cystic fibrosis of the pancreas would suggest that this diagnosis should not be made on the basis of duodenal trypsin activity alone. H. Shwachman *et al.* (*Am. J. Dis. Child.* **92,** *347* (*1956*)) estimate that duodenal trypsin may be present in 10 to 15 per cent of patients having a clinical course, and other findings, diagnostic of cystic fibrosis of the pancreas. Their studies are representative of those of other groups interested in cystic fibrosis. Varying degrees of pancreatic involvement in this disease were found. Out of 18 patients having normal trypsin activity in the duodenal fluid initially, four have died and eight have been followed sufficiently to demonstrate progress from a state of partial pancreatic enzyme deficiency to a complete one. These workers observed frequent dissociation of enzyme activity in the duodenal aspirate, with discrepancies between trypsin concentration and viscosity occurring often. They also noted a lack of correlation among trypsin, amylase and lipase activity as the disease progressed.

It has become apparent that pancreatic involvement in cystic fibrosis of the pancreas is not a constant feature of the disease, and that cases may succumb from respiratory involvement before the loss of pancreatic trypsin activity occurs. These data support the original hypothesis of the generalized disease, with the modification of including a disturbance of the sweat glands as an added and nearly constant feature. Consequently, determination of the sodium or chloride concentration in sweat (*Nutrition Reviews* **14,** *41* (*1956*)) has become an essential clinical tool in making this diagnosis. The studies of Bate and James would suggest that determination of the proteolytic activity of the duodenal fluid may become less important in the management of cystic fibrosis of the pancreas, but that this diagnostic technique probably has wider usefulness in gastrointestinal disturbances generally.

INTRAVENOUSLY ADMINISTERED CALCIUM IN PARATHYROID DISEASE

During the last few years there has been increased interest in the evaluation of parathyroid function. The use of intravenous calcium in assessing parathyroid status was an outgrowth of a study by C. H. Baylor, H. E. Van Alstine, E. N. Keutmann, and S. H. Bassett (*J. Clin. Invest.* **29,** *1167* (*1950*)) who noted a decrease in urine phosphorus following the administration of intravenous calcium. They suggested that the decrease in urine phosphorus reflected a suppression of parathyroid function.

Following this suggestion, J. E. Howard, T. R. Hopkins, and T. B. Connor (*J. Clin. Endocrinol. and Metab.* **13,** *1* (*1953*)) examined in detail the alterations in serum and urine phosphorus after an intravenous infusion of calcium gluconate. The dosage averaged 15 mg. of calcium per kilogram of body weight and was given over a four-hour period. In eight normal adults this resulted in an increase in serum calcium ranging between 1.3 mg. per cent and 5.8 mg. per cent. This increase was invariably accompanied by a rise in serum phosphorus, the peak serum phosphorus being noted by the end of the infusion, or during the four ensuing hours. By the next day, serum calcium and phosphorus levels were normal. The 24-hour urine phosphorus was always less on the experimental day than on the control day, although the serum phosphorus was elevated and the amount of phosphorus filtered at the glomerulus was proportionately higher.

As this situation is similar to that seen in hypoparathyroidism, where a normal or decreased urine phosphorus accompanies an increased serum phosphorus, this intravenous calcium test was used in three pa-

tients with surgical hypoparathyroidism. In these patients, the infusion of calcium gluconate led to an increase in serum phosphorus which was accompanied by increased urine phosphorus. This observation confirmed the postulate that the increase in serum calcium depressed parathyroid function, which in turn led to increased renal tubular reabsorption of phosphorus. Thus, in the hypoparathyroid patient, there is no change in tubular reabsorption of phosphorus, and the urine phosphorus increases as a result of the increase in serum phosphorus and the consequently larger filtered load.

Three patients with parathyroid adenomas displayed little change in urine phosphorus as a result of the infused calcium. This is in accord with the consideration that the parathormone secretion by an adenoma is essentially uncontrolled and is not affected by changes in serum calcium or phosphorus.

B. E. C. Nordin and R. Fraser (*Clin. Sci.* **13,** *477 (1954)*) performed similar studies and confirmed these findings. They also examined the effects of intravenous calcium in patients with osteomalacia in whom there was probably secondary hyperparathyroidism. These patients displayed the greatest decrease in urine phosphorus excretion, consonant with the view that the elevation of the serum calcium effected a cessation of the previously heightened parathyroid activity.

This cessation of parathyroid secretion may not be sufficient explanation for the changes observed, in view of a case reported by L. H. Kyle, M. Schaaf, and C. A. Erdman (*J. Lab. Clin. Med.* **43,** *123 (1954)*). These investigators, during their studies of the responses to intravenous calcium which were like those noted above, found that a child with idiopathic hypoparathyroidism and an elevated serum alkaline phosphatase displayed a normal response to intravenously administered calcium. The elevated alkaline phosphatase suggested the possibility of osteomalacia. Howard *et al.* (*loc. cit.*) and F. Albright and E. C. Reifenstein ("Parathyroid Glands and Metabolic Bone Disease", Baltimore, Md. 1948, pp. 126) had the same experiences with patients having similar conditions. The anomalous response to the infusion of calcium suggests that osteomalacia, *per se*, may alter the effects of intravenous calcium, although the elevation of serum calcium was seen to be the same as in the control groups.

Most recently M. F. Garcia, L. M. Espinar and O. E. de Landazuri (*Rev. Clin. Espanola* **60,** *87 (1956)*) studied the changes resulting from intravenous calcium loads using an infusion of saline on the previous day as a control. The excretion of calcium and phosphorus in the urine was followed at two-hour intervals. In the normal patients the excretion of phosphorus fell during the calcium infusion, rose during the two hours after the infusion was stopped, but was below the control values during the remainder of the 24 hours. This test in the one hypoparathyroid patient led to an increase in the urinary excretion of phosphorus, although the urine phosphorus excretion was low during the two hours following the calcium load. This phenomenon of an early rise in urine phosphorus has also been noted by W. P. U. Jackson, R. Hoffenberg, G. C. Linder, and L. Erwin (*J. Clin. Endocrinol. and Metab.* **16,** *1043 (1956)*) and whether this early rise in urine phosphorus is a more characteristic response to a calcium load than the subsequent drop in urine phosphorus is still to be determined.

In spite of this somewhat anomalous finding, the value of the intravenous calcium test in the diagnosis of hypoparathyroidism has been demonstrated by all of these workers, excepting the rare patient with an elevated alkaline phosphatase level. Although the mechanism of the decrease in urine phosphorus is plausibly explained, the rise in serum phosphorus has no adequate interpretation. The increase in serum phosphorus was noted in all patients and

could not be explained by the increment of urine phosphorus conserved as a result of the test. It is not probable that the excess of phosphorus comes from bone, since the concurrent hypercalcemia would favor deposition of bone salt. There must be other mechanisms by which the hypercalcemia affects either the entry of phosphorus into the extracellular compartment from intracellular sources or the equilibria between organic and inorganic phosphorus. In any event, this finding should lead to studies of heretofore unknown facets in the control of the serum phosphorus level.

SECULAR CHANGES IN HEIGHTS AND WEIGHTS OF CHILDREN

There are a number of reports, and many popular statements, indicating that the heights and weights of children are greater than they were in the past. These changes were emphasized in a study of the influence of World War II on German school children. P. E. Howe and M. Schiller (*Nutrition Reviews* **12,** *272 (1954)*) found that eleven-year-old boys were 3 inches taller and 3.3 pounds heavier in 1940 compared with similar children in 1920. For eighteen-year-old boys, the increase in height was 2 inches and in weight was 9 pounds.

J. B. de V. Weir (*Brit. J. Nutrition* **6,** *19 (1952)*) found that school children in Glasgow showed a progressive increase in height and weight over the period 1906 to 1949. The rate of increase, especially for weight, was relatively slow until after World War I. There was a suggestion of a deceleration in the rates during the depression in the early thirties. Over this period, the average increases in height for the school boys were: five-year-olds, just under 3 inches; the nine-year-olds, 4 inches; and thirteen-year-olds, 5 inches. The average increases in weight were: five-year-olds, 3 pounds; nine-year-olds, 7 pounds; and thirteen-year-olds, 14 pounds.

A study of the data on heights and weights led de V. Weir (*loc. cit.*) to conclude that the increased rates in both parameters resulted from a greater increase in the children who were most retarded. The increased rates in the children were reported to have resulted only in a lowering of the age at which physical maturity was attained but had no influence on the heights and weights of adults. The evidence for the latter statement is not given in the paper, and until such time as the data are presented, the conclusion cannot be accepted.

Some of the previous reports showing an increase in heights and weights of English children were open to question, according to A. W. Boyne, F. C. Aitken and I. Leitch (*Nutr. Abstr. and Rev.* **27,** *1 (1957)*). The primary deficiency in the earlier studies was the long interval of time between the points on the graph showing the secular trend. To fill in the gaps, Boyne, Aitken, and Leitch analyzed the height-weight records of English children for the period 1911–1953. The analysis was limited to the five, eight, and twelve-year-olds. Approximately a million school medical records were analyzed.

The records for primary school children led Boyne, Aitken, and Leitch (*loc. cit.*) to the conclusion that "county" (presumably rural) children are taller and heavier than urban children. It is difficult to calculate the differences and their significance from the curves, but it would appear that twelve-year-old "county" boys were 1 to 2 pounds heavier than urban boys.

A report by A. W. Tuxford and R. A. Glegg (*Brit. Med. J.* **I,** *1423 (1911)*) suggested that children in the south of England were taller and heavier than those in the north. According to Boyne, Aitken and Leitch (*loc. cit.*) the difference seen in the earlier study probably stemmed from the

higher percentage of rural children in the sample used for southern England. When Boyne, Airken, and Leitch compared the height-weight data for boys in a northern city (Sheffield) with that of those from a city in the south of England (Newport, Monmouthshire) there was no indication of any difference for the five, seven, and twelve-year olds.

The study by Boyne, Aitken, and Leitch (*loc. cit.*) showed that urban boys and girls were 2 to 3 inches taller at age five in 1953 than in 1913, and 3 to 4 inches taller at ages eight and twelve. The boys were 4 to 6 pounds heavier at age five, 7½ to 9 pounds heavier at age eight, and 14 to 17 pounds heavier at age twelve. The girls showed similar weight increases except for the twelve-year-olds, where they may actually have increased in weight by an additional 2 pounds (16 to 19 pounds). The increases in height and weight for the "county" children appeared to be slightly less than those for the urban children. The data for the "county" children are much less complete than those for the urban group, and so it is difficult to evaluate the magnitude of the changes. Throughout the period, however, "county" children were taller and heavier than their urban counterparts.

The curves for the urban twelve-year olds show a decrease in heights and weights just prior to World War I, followed by a gradual rise through the twenties. There is a suggestion of a plateauing of heights and weights during the depression of the early thirties. There was a more prominent plateauing of heights and weights for the eight and twelve-year-olds during World War II. From 1947 on, there was a sharp increase in weight gain of the twelve-year-olds with less acceleration in the five and eight-year-olds.

When Boyne, Aitken, and Leitch (*loc. cit.*) plotted heights of the children against their ages, they secured a series of lines, each of which represented the children born at ten-year intervals. The lines for the children born in successively later decades were higher than those for the preceding decades. For both boys and girls the lines for heights were parallel, except for those representing the children born in 1931 and 1941. In this case, the lines started at essentially the same point and then spread out. Except for the preceding, it would appear that the extra gain in height of the English children occurs before they are five years old. From then on they maintain this gain but do not add to it.

Similar curves for weight against age show a series of lines starting at essentially the same point and then fanning out. The extra gain in weight for both boys and girls occurred at a relatively slow rate up through the eighth year but from then on, it occurred at an increasing rate. The charts for the twelve-year-olds born in 1941 show them to be 5 to 6 pounds heavier than the twelve-year-olds who were born in 1931. The increase in weights of the other twelve-year-old groups born prior to 1931 was only approximately 2 pounds.

There is no one factor which can be singled out as the explanation for the increased rate at which English children, during the past half century, have been increasing in height and weight. Improved nutrition undoubtedly played some role in this phenomenon since beginning in 1907 there was an improvement in the milk supply, in 1920 rickets began to disappear, and in 1934 the school milk program was started. There were, however, concomitant improvements in community and personal hygiene which also contributed to the health of the children, and thus indirectly may have resulted in an improvement in growth rates.

The average heights and weights of the English boys and girls born in 1941 compare well with recent Canadian records. L. B. Pett and G. F. Ogilvie ("The Canadian Weight-Height Survey," *Body Measurements and Human Nutrition, J. Brozek, Editor, Wayne Univ. Press (1956)*) measured large numbers of a representative cross sec-

tion of the inhabitants of Canada during the spring and summer of 1953. They found the twelve-year-old Canadian boys about 2 pounds lighter than the English boys, while the Canadian twelve-year-old girls were 4 pounds heavier than their overseas cousins.

The increases in heights and weights of the English children are similar to those observed in the United States. J. M. Hundley, *et al.* (*Am. J. Pub. Health* **45,** *1454* (*1955*)), in a study of first-grade pupils in Philadelphia, found that the children who were born in 1942 were heavier by 2.6 to 3.5 pounds than those born in 1920. The latter agrees very well with the English data of Boyne, Aitken, and Leitch (*loc. cit.*). The data for Philadelphia show that the children in the area with the higher income families were taller and heavier throughout this period than those from the lower income area. The children from the economically favored area also showed the greater increase in weight over the years. The heights for the children from the economically underprivileged area showed a progressive increase, while the heights for the children from the economically favored area showed a suggestion of a dip during the depression of the early 30's.

The above studies are important since they document a trend in children's development which has become increasingly apparent over the years. These studies, involving a statistical analysis of the routine medical examinations made each year on millions of school children, suggest that greater use might be made of these records. Today most of them are filed without any attempt at tabulation. Why couldn't a mathematical study of these records be a fit project for high school students interested in science?

It is still not known whether the increased rate of gain in heights and weights of children is associated with an adult size which is taller and heavier than those of yesteryear. The paper by Boyne, Aitken, and Leitch (*loc. cit.*) states that another work of theirs is in progress in which they will examine fresh evidence on the age at which growth is completed. Perhaps from that work will come an answer to the question, "Are adults today taller and heavier than were their grandparents?"

CIRRHOSIS AND MALNUTRITION IN MAN

In a particularly challenging study of the problem of human hepatic cirrhosis, J. Higginson, B. G. Grobbelaar, and A. R. P. Walker (*Am. J. Path.*, **33,** *29* (*1957*)) come to the conclusion that the role of inadequate diet in the development of liver disease is not established in the South African Bantu. In this population severe fibrosing liver disease is widespread, and the diet is considered to be inadequate.

As a result of a large scale study based on 876 post-mortem examinations and 215 liver biopsies, however, these investigators report that there is little or no correlation between the state of nutrition of the Bantu and the severity of the liver disease. Furthermore, improving the diet of the Bantu for long periods of time seemed to have little effect on the incidence of hepatic disease. Fatty change, which so often appears to precede the development of so-called nutritional or alcoholic cirrhosis in America and Europe, was virtually absent in the adult Bantu. Many of the cirrhotic livers appeared to show a pattern suggestive of previous widespread necrotizing lesions, rather than the more uniform and finer fibrosis usually seen in cirrhotic livers where malnutrition is known to play a role. It would be tempting to try to relate the adult liver disease in the Bantu to the widespread Kwashiorkor occurring in infancy in these people.

However, Higginson *et al.* find that there is no evidence that hepatic fibrosis or cirrhosis develop from the Kwashiorkor

liver lesions. Furthermore, there was a definite age gap between the fatty liver of Kwashiorkor and the appearance of the more severe lesions of diffuse portal fibrosis which did not support a cause-effect relationship. Although there is little direct evidence to support it, the authors indicate that many of the lesions were similar to those seen following a viral hepatitis, and they suggest that widespread liver virus disease would explain their findings in the most satisfactory manner. They also suggest that a residual lowered metabolic reserve of the liver following hepatic disease in infancy, such as Kwashiorkor, may predispose the liver to other noxious agents, viral or otherwise.

After careful analysis of the nutritional factors involved in liver disease and the nutritional status of the Bantu, the authors conclude that "the high incidence of liver disease in the Bantu is far from being explicable on the basis of clear-cut and widespread nutritional deficiencies of these people."

CONGENITAL HYPOPLASTIC ANEMIA

A defect in tryptophan metabolism in congenital hypoplastic anemia, manifest by the presence of an abnormal metabolite of tryptophan, anthranilic acid, in the urine (*Nutrition Reviews* **12,** *102 (1954)*), has stimulated interest in possible nutritional therapy for this disease. Congenital hypoplastic anemia is an isolated deficiency of red blood cell formation dating from birth, in which the production of white blood cells and platelets by the marrow is unaffected. Children having this disease apparently grow and develop normally. Treatment in the past has consisted of repeated transfusions at intervals of four to eight weeks. Spontaneous remissions of variable duration have been known to occur. The essential defect in hematopoiesis would appear to be a failure of production of mature reticulocytes or erythrocytes.

Since treatment with ACTH or adrenal corticoids has been successful in hemolytic anemias and in other hypoplastic anemias, treatment of congenital hypoplastic anemia with ACTH and cortisone has been attempted. H. A. Pearson and T. E. Cone (*Pediatrics* **19,** *192 (1957)*) have reviewed the available literature and have noted in this seven successful responses, and three failures, with adrenal cortical therapy.

Their case was first seen at the age of eight weeks with a severe anemia of a normocytic normochromic type. The hemoglobin concentration was 2.25 g. per cent and the bone marrow showed only 4.2 per cent total erythroid precursors. The patient was given cortisone orally in doses of 50 mg. daily for 14 days without any response. At the age of nine months he was readmitted to the hospital for further study. On this admission he was treated with 10 mg. of intramuscular ACTH, four times daily. After five days of this therapy reticulocytosis occurred, the hemoglobin rose to near normal values, and the bone marrow was essentially normal in appearance. This hematologic response ceased two weeks following discontinuation of ACTH, but recurred on 50 mg. cortisone per day. Because of the development of Cushingoid facies, an attempt was made to reduce the cortisone dose to 37.5 mg. per day but the reticulocytes disappeared from the circulating blood and the hemoglobin began to decrease. Because the dose of cortisone seemingly necessary to maintain the child in remission was producing chronic toxicity, intermittent therapy was attempted. The child was given 125 mg. of cortisone per day for three days, followed by a four-day rest period. This regimen maintained his hemoglobin at approximately 9 g. per cent. Reticulocytes were present in the blood on the days during which cortisone was administered, but were absent during

the rest period. These observations would also suggest that there was a very definite threshold in the response of this patient's hematopoietic system to cortisone.

A qualitative test for the presence of anthranilic acid in the urine was positive seven days following discontinuation of the cortisone therapy. Following five days of cortisone treatment at a dose of 125 mg. daily, accompanied by reticulocytosis, the qualitative test for anthranilic acid was again positive. Although quantitative determinations were not done, there appeared to be no change in the amount of anthranilic acid found in the two determinations. There was no alteration in the patient's serum tryptophan concentration, which was 1.3 mg. per cent both before and after therapy. The 5-hydroxyindolacetic acid excretion was 1.9 mg. per 24 hours, which was within the limits for normal adults. Since the period in which these observations were made, the child had been maintained in remission for eight months on the regimen of interrupted cortisone administration.

The fact that patients with congenital hypoplastic anemia do respond to cortisone or similar therapy, and that spontaneous remissions are known to occur in this disease, suggests that the genetic absence of an enzyme or enzyme system essential for erythropoiesis is not the most likely explanation of this disease. On the other hand, the presence of an abnormal metabolite of tryptophan in the urine, which did not appear to be influenced by cortisone therapy adequate to produce a remission in the patient, would suggest that a genetic enzyme abnormality in tryptophan metabolism may be an essential feature of this disease. Such patients may well provide material suitable for the further elucidation of some of the intricacies of tryptophan metabolism in man.

ASCORBIC ACID AND BIOFLAVONOIDS

The literature on drug and dietary measures to prevent or alleviate colds has been replete with claims that were based on evidence that was inadequate to support the claims. In most instances, the experimental plan did not include reasonable provision against misinterpretation because of failure to have objective tests to appraise the treatment. Also, in a majority of these cases, reasonable precautions had not been taken to avoid subjective bias on the part of the observer or the test subjects. Recurrent claims for a vitamin function on the part of bioflavonoids have been based similarly on inadequate evidence, as reported officially by the American Institute of Nutrition and the American Society of Biological Chemists in denying a vitamin status for the bioflavonoids.

W. L. Franz, G. W. Sands and H. L. Heyl; H. E. Tebrock, J. J. Arminio and J. H. Johnston (*J. Am. Med. Assn.* **162,** *1224;* **162,** *1227 (1956)*), have reported on comprehensive, objective tests concerning the claims for usefulness of ascorbic acid and bioflavonoids in the treatment of the common cold. The first of the two studies was based upon observations through a 12-week period including a record of the incidence of colds and the therapeutic effect of administering the test materials, alone or in combination.

In a study of 89 medical students and nurses there was no evidence of an advantage from the proposed therapy in terms of either the incidence or the duration or severity of colds, nor was there any evidence that simultaneous administration of bioflavonoids had affected the blood levels of ascorbic acid. In summary, the authors reported:

> "We are reporting a controlled pilot study of the clinical effect of bioflavonoids and ascorbic acid (vitamin C) on the incidence and cure of the common cold, correlated with serial deter-

minations of blood ascorbic acid level on the 89 medical students and student nurses comprising the test group. The administration of a bioflavonoid had effect neither on the incidence or cure of colds nor on the ascorbic acid level of the blood."

The second study included observations on nearly 2000 subjects, most of whom were employed in industry. A number of students and private patients were included in the study with comparable results. In summary, the authors reported:

"The effect of 1 gm. of bioflavonoid and/or 200 mg. of ascorbic acid administered daily in aborting or curing the common cold was tested in a controlled double-blind trial on over 1900 subjects. The medicaments were given, either singly or in combination, in addition to the usual treatment used to alleviate symptoms. No appreciable effects were observed after three days on subjective or objective improvement; on disappearance of running nose, sneezing, cough, hoarseness, malaise, headache, postnasal drip, or sore throat; on decrease in nasal secretions or obstruction or pharyngitis; or in time lost from work. In our opinion neither of these drugs in the dosage given has any significant effect in altering the course of the common cold."

The authors have contributed a valuable record under conditions that merit confidence.

CALCIUM AND PHOSPHORUS IN LACTATION

Obvious as it is that calcium and phosphorus are intimately involved in lactation, the details of their interaction in this process have remained relatively obscure. Therefore, it is not too surprising that, with increasing availability of Ca^{45} and P^{32}, a number of laboratories have become active in the elucidation of some of these problems.

M. Kleiber and J. R. Luick (*Ann. N. Y. Acad. Sci.* **64,** *299 (1956)*) have recently reported on their studies of the lactating cow. Specifically, they were concerned with the requirements of calcium and phosphorus for lactation, the sources in blood of milk calcium and phosphorus, the site of synthesis of serine phosphate and casein, the relation of blood calcium and phosphorus to their source in the feed, and the regulation of the calcium supply flow.

Experiments involving the injection of labeled calcium and phosphorus salts into the bloodstream of cows indicated that calcium and phosphorus of milk can be derived from ionic forms of these elements in the blood. The maximum labeling of milk for P^{32} was reached at about five hours after injection. (This is also the approximate time of maximum labeling by Sr^{89} which is presumably a valid tracer for calcium). In another experiment it was found that a greater part of the injected Ca^{45} than of the injected P^{32} appeared in the milk over a longer period of time. Thus, following intravenous injection of Ca^{45} and of P^{32} into cows producing 53 to 66 kg. of milk in seven days, 35 per cent of the injected Ca^{45} and 22 per cent of the injected P^{32} appeared in the milk.

A collecting pool may sometimes lead to a product with a higher specific activity than that observed in the precursor at a given time. This is the case for calcium in the colostrum. The results of W. J. Visek *et al.* (*J. Dairy Sci.* **36,** *376 (1953)*) indicate that much of the injected Ca^{45} found in the colostrum probably entered the mammary gland at a time when the specific activity of the bloodstream was high, and remained there until the animal was milked.

The results of investigations by A. H. W. Aten and G. Hevesy (*Nature* **142,** *111 (1938)*) suggest that utilization of inorganic

P^{32} for casein synthesis occurs in the udder. However, the possibility exists that an organic precursor to casein is formed in the liver, or elsewhere. To investigate this possibility, M. Kleiber and J. R. Luick (*loc. cit.*) injected labeled phosphate into one cystern of a lactating cow. If all of the casein phosphorus were derived from inorganic phosphorus in a process which takes place outside the udder, the casein phosphorus from all quarters should have the same specific activity. The result of local injection was, however, that in the first milk samples, taken three hours after injection of the P^{32}, the casein from the injected quarter had a specific activity 11 times that of the specific activity in the casein from the three noninjected quarters.

The "true" digestibility of calcium in the diet varied from 17 to 56 per cent of the total calcium eaten. "True" digestibility is defined as a function of the calcium in the feed per day, the calcium absorbed per day, and the calcium secreted per day via the feces, the urine, and the milk. To make up a dietary calcium deficiency which may amount to as much as 9.0 g. per day during lactation (a dairy cow in high production may give off, daily, in her milk 43 g. of calcium and 37 g. of phosphorus), the cow mobilizes calcium from the skeleton. At the same time, phosphorus is mobilized from the bone. Obviously, if there is a reduction in available phosphorus and calcium, milk production will be affected.

The authors claim that mobilization of calcium from the bone seems to be the main means of regulating the calcium supply to the lactating gland. They base their notion for the existence of such a regulator on the great variability of "true" digestibility.

It was noted that the ratio of calcium to phosphorus in the diet, which apparently affects the activity of the parathyroid system, did not greatly affect the turnover rate of calcium pools, but did influence the size of the pools. Pool size was estimated by dividing an injected dose of Ca^{45} by the specific activity at any given time extrapolated to time of injection. Feeding a cow with a low calcium and high phosphorus ration before calving resulted in increased available calcium in the body pools but a decreased, rather than an increased, rate of turnover in these pools.

These studies provide excellent examples of the utility of radioisotopes in unraveling difficult metabolic problems. It is to be expected that within the not too distant future considerably more will be known of the nature and regulation of the calcium supply flow through the medium of this technique.

MOLYBDENUM AND UNIDENTIFIED TRACE MINERALS IN POULTRY NUTRITION

The importance of molybdenum in animal nutrition as a constituent of the enzyme xanthine oxidase, and as a possible essential element, has been reviewed (*Nutrition Reviews* **11,** *250 (1953)*; **14,** *315 (1956)*). It has been suggested that molybdenum may be an essential element since it reversed a growth depression and death loss produced by adding small amounts of tungsten to diets of chicks (*Ibid.* **14,** *315 (1956)*; E. S. Higgins, D. A. Richert, and W. W. Westerfeld, *J. Nutrition* **59,** *539 (1956)*). However, convincing and unequivocal proof that molybdenum is an essential trace mineral can be demonstrated only by well controlled experiments in which molybdenum-deficient diets (containing no mineral antagonists) are fed to animals with resulting manifestations of a deficiency, such as poor growth, pathological damage, or reproductive disturbance.

The study of B. L. Reid, A. A. Kurnick,

R. L. Svacha, and J. R. Couch (*Proc. Soc. Exp. Biol. Med.* **93,** *245* (*1956*)), in which growth responses were obtained with molybdenum in chicks and turkeys, is at least a partial answer to the above condition of proof of dietary essentiality of molybdenum. Previous studies from these and other laboratories, showing the need of an unidentified mineral for chickens, have been reviewed (*Nutrition Reviews* **14,** *51* (*1956*)).

Reid and co-workers (*loc. cit.*) used diets consisting of glucose, extracted soybean protein, glycine, and methionine, supplemented with all known vitamins and a salt mixture containing all known essential elements. The addition of only 0.0126 mg. of molybedenum per kilogram of diet, added as molybdic acid, caused an increase in growth up to 18.7 per cent in four-week experiments in replicated experiments with two groups of chicks. Also growth of the young turkey was increased 19.1 per cent with this same level of molybdenum in one replicated experiment. These growth responses were unexpected since the chick diet contained as much as 0.972 mg. of molybdenum and the poult diet contained 1.58 mg. of molybdenum per kilogram of diet by analysis (method of analysis was not given). The authors suggested that nearly all of this molybdenum must have been unavailable to the bird. The authors concluded that "under conditions of these studies a nutritional requirement for molybdenum by the chick and poult may be demonstrated."

A careful examination of the conditions of their studies gives no clear-cut explanation of the growth response to molybdenum other than a simple deficiency. Unfortunately, the authors did not state whether or not distilled water was used, nor did they indicate whether or not reagent grade salts were used. Also, it should be pointed out that the basal diet used for the chicks contained higher levels of certain ions than is considered normal. For instance, calcium was present at a level of 1.56 per cent of the diet (as supplied by 1.45 per cent of $CaCO_3$ and 4.21 per cent of $CaHPO_4 \cdot 2H_2O$). The basal diet also contained about 13 times the National Research Council's tentative recommended level of iron for poultry (as suppled by 0.16 per cent of ferric citrate) and 4.5 times the requirement of manganese (as present in 0.078 per cent of $MnSO_4 \cdot 1H_2O$). Whether these relatively high levels of minerals had any affect on the growth response of molybdenum is doubtful and remains to be proven. It is known that, for as yet unexplained reasons, plant and animal growth responses to molybdenum can be obtained under conditions of ion imbalance, such as in the presence of tungsten, copper, manganese, or sulfate ions (*Nutrition Reviews* **13,** *142* (*1955*); **14,** *315* (*1956*); **15,** *28* (*1957*); Higgins *et al.* (*loc. cit.*); and R. F. Miller, N. O. Price, and R. W. Engel, *J. Nutrition* **60,** *539* (*1956*)).

It is becoming increasingly apparent that still other trace minerals are required by the chick, and possibly other animals. For instance, recent unconfirmed reports suggested that bromine was essential for normal growth of chicks and rats (*Nutrition Reviews* **14,** *349* (*1956*)). In addition, growth effects have been obtained in chicks with sources of minerals added to diets in which molybdenum and bromine did not substitute for the ash (*Nutrition Reviews* **14,** *51* (*1956*); A. B. Morrison, R. Dam, L. C. Norris, and M. L. Scott, *J. Nutrition* **60,** *283* (*1956*)). These latter workers suggested that the unidentified mineral(s) was necessary for bone formation as well as for growth.

Because of the great importance, in the nutrition field and in the food industry, connected with any trace mineral proven to be essential, it is necessary that exhaustive proof be given along with any report of the essential nature of an element. The difficulties associated with disproving the essential nature of a substance, after a premature report of its need has appeared, are well known. For this reason such reports should be carefully examined and con-

firmed before they are finally accepted. On this basis one may conclude that molybdenum, as well as bromine, may be tentatively considered an essential trace element for growth of the fowl but that confirmation must be obtained before full status for these elements can be given.

These studies represent only a beginning in the complex field of trace mineral requirements and interrelationships. Future work, under still more rigorously defined conditions, will be necessary before the unidentified trace mineral picture becomes less complicated.

NUTRITION AND TOOTH SIZE AND SHAPE

Traditionally, the size and morphology of teeth have been considered to be dependent upon genetic factors. Numerous studies have shown that these characteristics are, to a large extent, passed from generation to generation through genetic influences. There has never been any experimental data to suggest that nutritional influences might modify genetically determined traits, until the recent studies by K. J. Paynter and R. M. Grainger (*J. Canad. Dent. Assoc.* **22,** *519 (1956)*). These investigators imposed varying nutritional situations upon young female rats prior to, or during, pregnancy and lactation.

The first group of control rats received a complete synthetic diet of the following percentage composition: sucrose 60, fat 4, agar 5, de-fatted casein 25, and a mineral mixture 5.7. This diet was supplemented with adequate amounts of thiamin, riboflavin, pyridoxine, calcium pantothenate, choline, inositol, and vitamins A and E. The second group of control female rats was fed laboratory chow throughout the entire experimental period. The females in the third group received the same synthetic diet as those in the first group but vitamin A was completely omitted from the diet for 3 months to deplete the animals' liver reserves of this vitamin. Just prior to mating and throughout pregnancy and lactation, 10 to 15 I.U. of vitamin A were provided per rat per day. The females in group four received the same synthetic diet as those in the first group, except that it was supplemented by drinking water containing 12 parts per million (ppm.) of sodium fluoride. The females in the fifth group received the same synthetic diet as those in the first group except that sufficient phosphate was added to change the normal 1:1 calcium-phosphorus ratio to 1:3, thus effecting a simulated vitamin D deficiency. Rats in this group received the high phosphorus diet for 3 weeks prior to mating and thereafter. The animals in group six received the same treatment as those in group five, except that the high phosphorus diet was begun 10 weeks prior to mating.

Each litter was weighed daily and the mean weight per litter recorded. All young were killed at 22 days of age and the jaws, right tibia, and knee joints were fixed in 10 per cent formalin. One half of the mandible and the tibia were decalcified and used for histological studies. The upper right molar of each specimen was dissected out and photographed under carefully controlled circumstances. Enlargements were made of each photograph with a final magnification of 26.5 diameters. These photographic enlargements were carefully measured by an assistant who had no knowledge of the identity of the teeth.

The offspring of the females fed the laboratory chow grew slightly more rapidly than the offspring of the females fed the complete synthetic diet. However, tooth sizes and shapes for the offspring of these 2 groups of animals were very similar. The offspring of the females maintained on the low vitamin A dietary regimen grew appreciably more slowly than the offspring of either of the first 2 groups. For example, on the fifth day, the average weight of the offspring in the low vitamin A group was 6.6

g., in comparison to 8.8 g. for the offspring of the synthetic diet group and 9.7 g. for the offspring in the laboratory chow group. Tooth sizes were appreciably smaller among the young rats in the vitamin A low group. For example, the mesial-distal distance in the cervical region was 74.4 units for the low vitamin A rats and 77.4 units for the offspring of each of the other groups. This reduction in tooth size was approximately proportional to the reduction in weight noted among the vitamin A low animals. In the fourth group where the females received the synthetic diet plus 12 ppm. of fluoride in the drinking water supply, the offspring grew slightly more rapidly than even those in the laboratory chow control group, with each animal at 5 days of age weighing an average of 10.3 g. Even though the animals grew as rapidly under the fluoride supplementation regimen, the dimensions of the first molar were appreciably lower than those of the control group, and almost as low as those in the vitamin A deficient group.

In group five, with the high phosphate diet for the shorter period of time, the offspring grew almost as well as those in the fluoride supplemented group and again there were almost identical decreases in first molar dimensions to those observed among the fluoride group. Where the high phosphate diet was fed to the females in group six for a longer period, the body weights of the offspring were appreciably lower than those of the control animals and almost as low as those in the vitamin A deficient group. However, tooth dimensions of the offspring in this group were the smallest of any noted in the other groups, with the mesial-distal dimension in the cervical region being 71.4 in contrast to the value of 77.4 noted among the control animals. In addition the depth of the mesial fissure of the first molar was less, and the angulation of the sides of the fissure was greater, than those either of the experimental or control groups. Although there were changes in the epiphyseal disc that were indicative of a vitamin D deficiency, in this group, the teeth appeared to be normal histologically. In addition, the bony trabeculae on the diaphyseal side of the epiphyseal plate were shorter and thicker than normal, and the rows of chondrocytes on the zone of proliferation in the discs had lost some of their typical linear orientation.

In a second experiment of an exploratory nature, the groupings of rats were arranged in order to test the influence of an interaction between fluoride in the drinking water and the calcium-phosphorus imbalance, and between fluoride in the drinking water and vitamin A deficiency. Unfortunately the effectiveness of this experiment was destroyed in large part by a severe pulmonary infection that led to many deaths among the offspring. However, the results, in general, corroborated those of the first experiment. In addition, the data indicated that, when fluoride was given in addition to a calcium-phosphorus imbalance or in addition to a vitamin A deficiency, there was a still greater reduction in tooth size than when either of these dietary manipulations was imposed singly.

The results of these studies raise a number of questions about the exact mechanism whereby the change in size and morphology was mediated. In view of the variety of variables that resulted in smaller teeth, and the fact that their influences appear to be additive, the result may have been caused by some nonspecific intermediate mechanism. Did these changes result in teeth of greater density or of changed chemical composition? Since this level of fluoride ingestion was below the level needed in rats to produce caries-resistant teeth, the question arises as to whether higher levels of fluoride would have caused still smaller teeth. Additionally, are the teeth of individuals who grow up in areas where there is fluoride in the water supply smaller or of different morphology than those of children in non-fluoride areas? If there is such a relationship, to

what extent is this reduced tooth size the cause for the reduced dental caries-susceptibility? These are unanswerable questions at present but ones that suggest the need for intensive investigation in this interesting field.

SUGGESTED PRECAUTIONS FOR TESTING FOOD CONTAMINANTS AND ADDITIVES

W. C. Hueper (*A.M.A. Arch. Path.* **62,** *218 (1956)*) attempts to clarify the food factors which should be investigated and outlines ways of evaluating the hazards which may exist as a result of non-nutritive substances in foods. Previously he had divided the dietary substances to be studied into food "additives" and food "contaminants" (*A.M.A. Arch. Path.* **58,** *360, 474, 645 (1954)*). The additives consist of at least 20 different classes of chemicals which include dyes, antioxidants, flavoring agents, bleaches, softeners, emulsifiers, and the like. The contaminants include at least 17 different categories such as pesticides, antisprouting substances, antibiotics, chemical sterilizing agents, household detergents, radioactive materials, and similar substances. Hueper summarizes his views on the need for long-term testing and outlines the difficulties involved.

If rigid public health controls were imposed and the 11-point testing program suggested by Dr. Hueper were adopted, it would require several years to give a proposed chemical a clean bill of health. Clearly, a screening method is needed which produces a quick and clean-cut answer as to whether a chemical is potentially carcinogenic. That there is need for further knowledge of the potential hazard of food additives and contaminants can hardly be denied.

Dr. Hueper sets up some guide posts which may help to decide which compounds should be most suspected and what tissues should be exposed to the compound in testing. Until more knowledge is available, he suggests that the number of food additives be limited to the smallest number possible and that labeling practices be improved. In other words, every effort should be made to avoid a "captive" population which has little basis for a choice as to whether it consumes natural food products or those which have potentially dangerous additives.

Using synthetic food dyes as a model, Dr. Hueper attempts to outline a cancer research program which would yield the greatest amount of useful knowledge concerning the hazards of these compounds to the producer, processor, handler, and consumer. He begins by suggesting that definite standards of purity be adopted on the basis of accepted tests of chemical structure, toxicity, and bioassay. This would make it possible to make direct conclusions regarding the effects of these substances in man and experimental animals. The results would not be so likely to be clouded by the question of whether a dye or a contaminant were responsible for observed results. The next point considered is the importance of toxicity data and the problems involved in interpretation of such data in regard to carcinogenesis. Hepatoxic, estrogenic, allergenic, or mitotoxic characteristics are listed as being particularly important in revealing possible carcinogenic properties and are illustrated by several examples from the dyestuffs. But the equally important dichotomy between toxic manifestations and carcinogenic properties is characterized by the very potent carcinogen 2-naphthylamine which has remarkably low toxicity.

The problems involved in a bioassay of dyes for carcinogenicity are carefully considered. Pointing out that qualitative tests are more important than quantitative ones, Dr. Hueper suggests that young animals of

several species should be employed and that the dyes should be tested over long periods in maximally tolerated quantities. Both oral and parenteral administration should be tested and in some experiments the conditions should be similar to those in which the dye will be ingested by man. Female animals should be utilized before and during repeated pregnancies to measure effects on the offspring. Metabolically deranged animals with induced abnormalities of the liver, kidney, thyroid, gastrointestinal tract, adrenal and pancreas which simulate chronic human disease should have a place in such studies since dyes may have quite different carcinogenic effects in diseased people as compared to normal ones. Finally, Dr. Hueper points out the value of epidemiological and biochemical studies on human populations. The difficulties of such studies are outlined and the particular importance of studying the workers in industries where certain dyes are widely used is emphasized. Furthermore, it is suggested that exposure data from patients showing multiple malignancies may yield some evidence of dyes or other compounds which are particularly hazardous.

SOURCES OF B_{12} FACTORS

One of the most promising sources of this family of vitamins has proved to be the dry solids from sewage sludge, in which the true vitamin may be present to the extent of 2.4 micrograms per gram (*Nutrition Reviews* **13,** *113 (1953)*).

In a series of recent papers, H. Y. Neujahr and co-workers have reported the results of investigations of the factors present in this source. Formation of various factors in digested sludge was found to be a very complex process (H. Y. Neujahr, *Acta chem. Scandinav.* **9,** *622 (1955)*), the formation of cyanocobalamin proceeding in several stages with participation of different organisms. It was found that factors C_2 and C_1 were produced in the early stages of fermentation and were then utilized in the formation of other factors. During intermediate stages, cyanocobalamin was used and factor B (cyanocobalamin minus the nucleotide) was produced. In the final stages, this was utilized and cyanocobalamin, pseudo B_{12} (containing adenine instead of 5,6-dimethylbenzimidazole) and factor A (containing 2-methyladenine) were produced.

In a separate study (*Ibid.* **9,** *803 (1955)*) the author found that "activated" (aerated) sludge was the best source of true vitamin B_{12} factors and that the source of the sewage was of prime importance to the amounts of the various factors.

In a recent series of experiments (*Ibid.* **10,** *917 (1956)*), Neujahr has investigated the isolation, from this source, of 11 B_{12}-klie factors.

Factors were separated by chromatography on cellulose columns or paper, and were partially characterized by ultraviolet absorption spectra, partition coefficients, paper electrophoresis, and microbiological assay with E. Coli and Ochromonas malhamensis. Only in the case of cyanocobalamin was enough material obtained to crystallize. Of the 11 factors isolated, only three gave a color test typical of nucleotide-containing factors (red with cyanide at pH 6.5) while 8 did not (violet color).

The factors isolated were: cyanocobalamin (vitamin B_{12}), B, V + W, X_1, X_2, X_3, X_4, Z_1, Z_2, Z_3 and Y. Factor Y was inactive and should not be included as a B_{12} factor. Z_3 appeared to be identical with C_1. Of the nucleotide-containing factors, W and V showed activity for E. Coli equivalent to that of cyanocobalamin and for Ochromonas about 50 per cent of that of cyanocobalamin. Of the non-nucleotide-containing factors, B, Z_2 and Z_3 had pronounced activity for E.

Coli while the X factors and Z_1 were inactive. None of the non-nucleotide-containing factors was active for Ochromonas.

The author pointed out that some of the factors may have been artifacts. It is unfortunate that too little material was available from these experiments (100 L of sludge containing 10 per cent dry solids) for a complete characterization and comparison with other known factors. It is to be hoped that further experiments along these lines will serve to clarify the nature of the many factors isolated from this useful source.

The multiplicity of factors relating to vitamin B_{12} has resulted in some confusion as to the specificity of B_{12} activity. This has been heightened by the diverse methods of bioassay, the various systems of naming, and the many sources of the factors. Actually, the bioassay with Ochromonas has been found to give a spectrum very similar to that of the more cumbersome assays using higher animals; there seems to be general agreement that only those factors active for higher animals should be designated as vitamins, all others being termed "pseudo B_{12}" factors. There is also fairly general acceptance of the fact that, regardless of the immediate source of the factors, they were probably ultimately synthesized by bacteria or actinomycetes (G. Briggs and F. S. Daft, *Ann. Rev. Biochem.* **24,** *339 (1955)*).

STUDIES OF LENS PROTEINS

Among all animal species that have been studied, changes in the refractive index of the lens are concomitant with the aging process. Chemically, these changes during aging are paralleled by decreasing water content and increasing insoluble albuminoid protein. The simplicity of lens structure led Z. Dische, E. Borenfreund, and G. Zilmenis (*Arch. Ophth.* **55,** *471 (1956)*) to investigate carefully the detailed changes in protein content of the rat lens during aging.

Sprague-Dawley rats from 35 days to 1060 days of age were studied. The lens weight increased rapidly during the first year of life and after one and one-half years, there was little further change in lens weight. The total amount of protein in the lens increased both absolutely and in percentage during the first half of life; thus, there was a relative loss of water.

The proteins were divided into soluble and insoluble fractions on the basis of solubility in distilled water. In the 35-day-old rat, insoluble protein comprised but one-seventh of the total protein. During the next 40 days, more soluble protein was formed than insoluble protein, but following this period the rate of accretion of soluble protein decreased whereas the insoluble protein continued to increase. As the total protein remained fairly constant after 150 days, the increase in insoluble protein was balanced by a decrease in soluble protein.

It was postulated by the authors that these protein changes in an ectodermal structure may be analogus to keratinization in the skin, and they therefore sequentially analyzed the lens for cysteine and cystine. The soluble proteins contained no cystine. The sum of the cysteine and cystine in the total lens remained the same after the initial growth period. Thus, the continuous increase in cystine content of the insoluble proteins suggested that the cysteine in the soluble protein was oxidized to the cystine of the insoluble protein.

The aging of the lens, therefore, was associated with the continuous net oxidation of the cysteine of the lens protein to cystine with continuous precipitation of albuminoid. It is known that the formation of cataracts is associated with an increase of the insoluble protein. Accordingly, Z. Dische, E. Borenfreund, and G. Zilmenis (*Ibid.* **55,** *633 (1956)*) examined the biochemical changes seen during induction of

cataracts in rats by galactose. When the rats were placed on the galactose diet for 21 days, there was no further increase in soluble protein. The accumulation of insoluble protein, however, was not altered by the diet.

It cannot be determined from these studies whether there was inhibition of synthesis of soluble protein or increased breakdown. The authors speculated about the significance of these changes in the genesis of cataracts and the analogies between the protein changes occurring in the skin and in the lens. These investigations demonstrated the usefulness of a simple structure, the lens, in examining some of the parameters of aging, and they opened new lines of study on this problem.

RUBIDIUM IN THE DIET OF RATS

Although rubidium is not recognized as a dietary essential for animals, there is interest in its possible nutritional or physiological effects. The biological effects of rubidium assume an added interest since its radioactive form (Rb-86) is used as a tracer for potassium (W. D. Love, R. B. Romney and G. E. Burch, *Circulation Research* **2,** *112 (1954)*; S. A. Threefoot, C. T. Ray and G. E. Burch, *J. Lab. Clin. Med.* **45,** *395 (1955)*; and G. E. Burch, S. A. Threefoot and C. T. Ray, *Ibid.* **45,** *371 (1955)*).

Workers at the Kansas Agricultural Experiment Station, Manhattan, have undertaken studies to determine the influence of varying levels of rubidium, with varying levels of the alkali metals, sodium and potassium, in the diet of rats (B. L. Glendening, W. G. Schrenk and D. B. Parrish, *J. Nutrition* **60,** *563 (1956)*).

On a purified diet composed of sucrose, casein, corn oil, and added minerals and vitamins, the effect of rubidium was investigated when the diet was low in sodium. The addition of 0.2, 0.3, and 0.4 per cent of rubidium to the diet reduced the growth rate and survival time of weanling rats. This was true both in the presence and absence of dietary additions of sodium. An interrelationship between the two metals was apparent, however, since rats receiving 0.2 per cent of sodium in the presence of rubidium grew better than, but did not survive as long as, those not receiving sodium. At the rubidium level of 0.3 per cent, for example, the mean survival time was increased from 17 days to 37 days by omitting the sodium from the diet.

Rubidium toxicity was evidenced initially by failure of normal body weight gains. Subsequent symptoms included a skin color change to a blue or purple tinge, especially around the neck and ankles. The rats assumed humped-up appearances, were sensitive to noise and touch, and often went into convulsions from the excitement of handling. These observations are in general confirmatory of earlier studies on the symptoms of rubidium toxicity in rats (R. H. Follis, *Am. J. Physiol.* **138,** *246 (1943)*; and P. H. Mitchell, J. W. Wilson, and R. E. Stanton, *J. Gen. Physiol.* **4,** *141 (1921)*).

Rats that survived the initial experiment were allowed to mate and reproduce. The 0.1 per cent level of rubidium allowed normal mating and gestations, but the young failed to survive after birth. Further reproductive studies indicated that a dietary level of 0.02 per cent of rubidium resulted in some survival of young, but there was an indication that females failed to raise normal litters when the diet was also low in sodium (0.02 per cent of the diet).

Since, in the above described studies, Glendening and associates had used a dietary level of 0.29 per cent of potassium, further studies were conducted in which

both sodium and potassium levels were varied in the presence of added dietary rubidium. Rats consuming the diet nearly devoid of all three elements survived an average of 53 days. Adding 0.25 per cent of rubidium to the diet decreased survival time to 23 days, whereas the addition of the same amount of sodium resulted in a survival time of 37 days. Potassium addition alone (0.25 per cent), on the other hand, increased survival time to 99 days. Further rubidium addition again reduced the survival time of the potassium-fed rats.

Post-mortem studies were routinely conducted, but the results were inconclusive as to the cause of death. Animals receiving no alkali metal except sodium were usually bloated before death occurred, and post-mortem examination indicated that edematous fluid had accumulated in the body cavities.

As would be expected, an increase in any of the alkali metals in the diet resulted in an increased tissue concentration of that element. Potassium in the diet reduced tissue sodium concentration. In general rubidium had a similar, but less marked, effect on the tissue sodium content. Rubidium similarly tended to reduce tissue potassium concentration, except in brain tissue. Rubidium appeared to be distributed throughout the body tissues like the other alkali metals. Its concentration in bone appeared to be lower than that in soft tissues.

Rubidium resembled potassium in that it accumulated to a greater extent in the blood cells than in the plasma. The path of rubidium elimination also followed that of the other alkali metals, namely via the kidneys.

Although the studies of Glendening and associates do not establish whether or not rubidium should be considered a dietary essential, they do support the view of a metabolic similarity with potassium and thus support the propriety of using Rb-86 as a tracer of potassium. Since a combination of sodium and rubidium resulted in better growth than did sodium alone, although inferior to the sodium-potassium combination, the authors suggest that rubidium can possibly serve as a limited substitute for potassium in the diet.

Since rubidium is a heavier metal than either sodium or potassium, the molar intake of rubidium, on diets containing 0.25 per cent of these metals, was only one-fourth that of sodium and one-half that of potassium. Molar concentrations of rubidium in tissues were, however, consistently higher than those of either of the other two metals. This would indicate that rubidium is preferentially retained by tissues and thus not entirely similar in its behavior to potassium. In this connection it should be mentioned that absolute reliance on the metabolic similarity of potassium and rubidium has also been questioned in *in vitro* studies of erythrocyte electrolyte metabolism with the use of Rb-86 (W. D. Love and G. E. Burch, *J. Lab. Clin. Med.* **41,** *351 (1953)*). The Kansas studies again emphasize that interactions, with respect to minerals, must be recognized in formulating diets.

DIETARY FAT AND CHOLINE DEFICIENCY

It has been known since the work of H. H. Channon and H. Wilkinson (*Biochem. J.* **30,** *1033 (1936)*) that the level of liver fat in choline deficient rats was influenced by the nature of the fat which was fed. The highest liver fat levels were observed when long chain saturated fatty acids were fed. This observation has been confirmed recently with purified low protein diets (D. A. Benton, A. E. Harper, and C. A. Elvehjem *J. Biol. Chem.* **218,** *693 (1956)*). The addition of 20 per cent butter or lard to a basal diet

containing 0.15 per cent choline chloride caused a much higher liver fat content than did similar amounts of margarine or corn oil. The omission of choline from the diet, or a reduction of the protein content, greatly increased the difference in liver fat between rats fed vegetable and animal fats. The fatty acids of butter were divided into solid and liquid fatty acids and re-esterified. Only the solid fatty acids were active in increasing liver fat. The view that long chain fatty acids were more lipogenic than unsaturated fatty acids was supported by experiments in which the effect of feeding oleic acid glycerides was compared to a mixture of oleic and stearic glycerides.

Further information concerning the influence of saturated and unsaturated fats on liver fat in choline deficiency has been provided by D. A. Benton *et al.* (*Proc. Soc. Exp. Biol. Med.* **94,** *100 (1957)*). The authors compared the effect of butter fat and corn oil in rats receiving different levels of choline in the diet. The basal diet was a highly purified low protein ration supplemented with all known vitamins and growth substances except choline. The fat of the diet was provided either as 30 per cent butter fat or corn oil. After a two-week experimental period the animals were killed and the liver fat determined. In the first experiment the effect of increasing concentrations of choline on liver lipid of rats eating the two different types of fat was evaluated. Although choline reduced the level of liver fat in both dietary groups, it did so at a level of 0.12 per cent choline chloride in the food of the corn oil-fed rats and 0.15 per cent of the butter fat-fed rats. Another difference between the corn oil and butter fat groups was observed in the rats on low choline rations; growth was considerably slower on corn oil.

In a second experiment, the basal diet was supplemented with methionine and tryptophan because the content of these amino acids is low in the basal diet. Methionine and tryptophan provoked a much greater growth in the absence of choline, but the liver fats were elevated more in the group of rats fed butter fat than in the group fed corn oil. Restoration of relatively normal liver lipid level again occurred with the addition of 0.12 per cent choline in the corn oil fed group, whereas 0.15 per cent was required with butter fat. Growth, however, was greater in the butter fat groups in the presence of marked choline deficiency. The addition of cystine to the basal diet did not increase the growth rate in rats fed either butter fat or corn oil, and was associated with a considerable mortality. With cystine the liver fat in the rats fed corn oil was higher than in comparable groups without cystine. With the addition of choline to a cystine containing diet, restoration of normal fat levels occurred again at lower levels in the corn oil fed rats.

Lesions of choline deficiency were found in the kidneys of rats not receiving choline. They were greatest in those rats showing the poorest growth, and in most cases these were the rats which were receiving corn oil.

These experiments indicate that the amount of fat deposited in the livers of rats fed a choline-deficient and protein-deficient diet is influenced by the type of dietary fat. The apparent requirement for choline needed to restore normal liver fat concentration is greater in the rats fed a saturated fat such as butter fat as compared to an unsaturated fat such as corn oil. The lower liver fat in the choline deficient rats fed corn oil and the restoration of normal liver fat with smaller amounts of choline should not be looked upon as necessarily beneficial or taken to mean that choline is spared by corn oil. In terms of growth, and the degree of kidney damage, corn oil appeared to have a detrimental effect. Despite the great interest in the special significance of unsaturated fatty acids, a rational explanation for these results in choline deficiency cannot yet be provided.

NUTRITION OF THE BLOWFLY

Information about the nutrition of insects has accumulated very slowly. However, during the past ten years several species have been reared on highly purified diets which permit detailed studies of nutritional requirements (A. J. McGinnis, R. W. Newburgh, and V. H. Cheldelin, *J. Nutrition* **58,** *309 (1956)*). With the tremendous diversity exhibited by insect species it would be surprising if, as in nutritional studies with microorganisms, further investigations on the requirements of insects did not bring to light a number of new nutritional interrelationships.

One development of considerable interest in this regard was the discovery that carnitine (vitamin B_T) is a growth factor for the yellow meal worm, *Tenebrio molitor* (*Nutrition Reviews* **13,** *24 (1955)*). Investigation of possible metabolic relationships between this betaine of beta-hydroxy-gamma-amino butyric acid and other biologically important methyl-containing compounds, such as betaine and choline, have been undertaken for only a few species and should prove of interest generally, as well as in the field of insect nutrition specifically.

Another important aspect of insect nutrition that has as yet received little attention is amino acid interrelationships. (Using a chemically defined medium that permits normal development of the blowfly, *Phormia regina*, (McGinnis *et al., Loc. cit.*) E. Hodgson, V. H. Cheldelin and R. W. Newburgh (*Canad. J. Zool.* **34,** *527 (1956)*) have studied the relationship between choline and certain related compounds in this species and have investigated, in somewhat more detail, its amino acid requirements.

The procedure used in this study consisted of raising the insects under sterile conditions from the egg stage to maturity. Previously the change in length of the larvae during development was used as the measure of growth, but in the present study change in weight was found to be a more reliable criterion. The basic diet consisted of a mixture of 18 amino acids, all of the known B-vitamins except vitamin B_{12}, a mineral mixture, ribonucleic acid, and cholesterol. These were dispersed in water, agar was added, and the medium was poured into tubes which were then sterilized in an autoclave. The sterile tubes were allowed to set in a slanting position. Sterilized eggs of *P. regina* were placed on the agar slants, which were incubated at 30°C.

The growth of larvae reared on the amino acid medium was slower than that of comparable organisms receiving casein instead of the amino acids. Nevertheless, similar larval lengths and weights were attained at pupation. The amino acid medium had the advantage of permitting unlimited variations in the amino acid components.

The omission of choline from the diet resulted in an extremely slow rate of growth, generally under 2 mg. in seven days, compared to a gain of 10 to 12 mg. when choline was provided. Substitution of carnitine for choline permitted normal growth, but betaine was without effect. Choline could also be replaced satisfactorily by 2,2-dimethylaminoethanol. It would thus seem that the larvae of *P. regina* can use methionine as a source of methyl groups for choline synthesis when 2-2 dimethylaminoethanol is provided. Since the methyl groups of betaine are thought to become available for choline synthesis only after being passed to methionine, further experiments to determine whether choline and methionine can be replaced by betaine, homocysteine, and 2,2-dimethylaminoethanol would be of interest.

This is particularly so in view of the observations with the cockroach, *Blatella germanica*, which suggest a direct conversion of betaine to choline (*Nutrition Reviews* **7,** *219 (1949)*). Also, since *P. regina* can synthesize carnitine when reared on a carnitine-free medium (G. Fraenkel, *Biol.*

Bull. **104,** *359 (1953)*), this organism should be a valuable tool for the study of choline-carnitine relationships, particularly if it is used in conjunction with other species which show differing requirements for these and related compounds.

With regard to amino acid requirements, McGinnis *et al.* (*Loc. cit.*) found, by omitting one amino acid at a time from the medium, that the ten amino acids that were essential for the growing rat were also required by *P. regina*. In the present study, however, the larvae failed to grow when provided with only the ten essential amino acids. The omission of alanine, glycine, hydroxyproline, and tyrosine from the mixture of 18 amino acids was without effect, but the omission of aspartic and glutamic acids severely retarded growth. It is therefore evident that either one of these is also essential for this organism.

The relatively short time required for this organism to reach maturity, together with the small quantities of amino acids required in the medium, should make it a valuable tool for studying dietary interrelationships among the amino acids. Studies of amino acid imbalances, toxicities, and antagonisms with *P. regina* larvae might well provide information that would speed and simplify the similar studies with higher animals.

The ease with which this insect and a number of other species can be raised under sterile conditions makes them ideal objects for studying the nutritional effects of microorganisms. The dietary requirements are basically similar to those of higher animals, and the ease of manipulation should make it possible to infect them readily with pure strains of bacteria. The use of larvae of the order diptera (flies) presents some problems because the agar medium used for raising them would probably permit the growth of bacteria in the external medium. However, the use of species from the orders blattaria (roaches) or coleoptera (beetles), in which the immature forms have biting mouth parts and which can be raised on dry diets that would not support microbial growth, would circumvent this problem.

Although the work reported by Hodgson *et al.* is of a preliminary nature, it points up the fascinating developments that can be expected in the expanding field of insect nutrition. Not only can fundamental developments in the biochemistry of nutrition be anticipated, but practical developments (such as the breeding of varieties of plants lacking essential growth factors for insect pests) may well follow from fundamental studies of insect nutrition.

NOTES

Nutritional Requirements of the White-Tailed Deer

Studies at the Pennsylvania State University, University Park, are underway to establish the nutritional requirements of the white-tailed deer (C. E. French *et al. Penn. Agr. Exp. Sta. Bull. 600 pp., July (1955)*). Young male fawns were raised chiefly on raw whole milk, calf starter, and alfalfa hay until six months of age. They were then fed rations ranging from being complete to deficient in calcium, phosphorus, energy, or protein.

Energy requirements for growth of a 150 pound deer were estimated to be about 9,900 Calories daily, or 5 to 6 pounds of air dried feed.

Although quantitative requirements were not definitely ascertained, the calcium requirement appeared to exceed 0.09 per cent (dry ration), and the phosphorus requirement was in excess of 0.25 per cent.

Body growth took preference over antler

development when the ration was limiting in calcium and phosphorus. Only on the complete ration did the deer develop large branched antlers (6 to 8 points and 12- to 15-inch main beams of 1 inch diameter above the base).

Although the browsing habits of deer are fairly well known, little work of the type now underway at Pennsylvania State University has been attempted. In many deer ranges in the United States there is a shortage of browse for adequate nutrition of the deer population, as evidenced by very low carcass weights of legal animals taken during hunting seasons.

Aqueous Humor Ascorbic Acid

It has been demonstrated by many investigators that the ascorbic acid concentration in aqueous humor is maintained in excess of that in blood. Three mechanisms have been proposed: 1) There is direct synthesis of ascorbic acid by the lens; 2) Dehydroascorbic acid is transported by the cilial epithelium, and is then reduced by the lens to ascorbic acid; 3) Ascorbic acid is actively concentrated by the ciliary epithelium. The reason for invoking the activity of the lens was the finding reported by several investigators that in aphakic eyes (without lens) the concentration of acqueous humor ascorbic acid was lower than in normal eyes.

E. F. Purcell, L. H. Lerner and V. E. Kinsey (*Arch. Ophth.* **51,** *1* (*1954*)) reinvestigated this problem, removing aqueous humor from normal patients and from patients with cataractous lenses. Simultaneously, plasma was obtained for ascorbic acid analysis. Between the two groups of patients there was a wide variation in the ascorbic acid concentrations of aqueous humor and plasma. The average concentration of aqueous humor ascorbic acid was lower than in normal and the plasma concentrations were also lower. Thus, the ratio of aqueous humor ascorbic acid to plasma ascorbic acid did not vary between the two groups. This ratio was 20 to one.

The fact that the concentration of ascorbic acid in the aqueous humor varied with that of the plasma in normal and aphakic eyes suggests that the lens did not participate in maintaining the concentration difference.

B. M. Chatterjee and B. P. Ghosh (*Arch. Ophth.* **56,** *756* (*1956*)) carried out a similar study utilizing normal patients, cataractous patients, and aphakic patients. Although the content of aqueous humor ascorbic acid was lower than in the previous study, there was essentially no difference among the three groups. The ratio of aqueous humor ascorbic acid to plasma ascorbic acid was approximately the same in all the patients with lens disease, but was unexplainably lower in the two normal groups. Nevertheless, the substance of the study is to support further the role of the ciliary epithelium in maintaining the higher concentration of ascorbic acid, and to re-emphasize the lack of participation of the lens in this phenomenon.

The Reversal of Penicillamine Toxicity with Ethanolamine or Pyridoxine.

The feeding of L-penicillamine to rats results in growth inhibition and frequently provokes convulsive seizures. These toxic manifestations were shown to be prevented by ethanolamine, and less effectively by monomethylethanolamine, dimethylethanolamine, or choline (J. E. Wilson and V. du Vigneaud, *Science* **107,** *653* (*1948*); *J. Biol. Chem.* **184,** *63* (*1950*)). Noting the similarity of the signs of L-penicillamine toxicity to those of pyridoxine deficiency in rats, E. J. Kuchinskas and V. du Vigneaud (*Arch. Biochem. Biophys.* **66,** *1* (*1957*)) investigated the effects of extra dietary pyridoxine on L-penicillamine toxicity.

When rats were fed a purified diet containing 0.35 per cent L-penicillamine hydrate and 1 mg. per cent pyridoxine, they lost weight rapidly. Increasing the dietary

pyridoxine to 10 mg. per cent allowed normal growth. Following the administration of tryptophan, rats receiving penicillamine and the low level of pyridoxine excreted large quantities of xanthurenic acid. This defect in tryptophan metabolism was corrected by increasing the dietary pyridoxine to 10 mg. per cent. The requirement of pyridoxine for normal tryptophan metabolism is well established (*Nutrition Reviews* **3,** *72 (1945)*).

These results demonstrate that the feeding of L-penicillamine to rats increases the pyridoxine requirement. The observation that penicillamine toxicity may be alleviated by either pyridoxine or ethanolamine is of considerable interest and suggests a metabolic relationship between these substances.

Recent Nutrition Books

How to Increase the Industrial Use of Corn. The President's Appointed Bipartisan Commission on Increased Industrial Use of Agricultural Products. Report of the Committee for Industrial Corn Mill, January 1957. Pp. 17.

Food Hygiene: *World Health Organization Technical Report Series.* Expert Committee on Environmental Sanitation, Fourth Report, 1956, No. 104, pp. 28. Available also in French and Spanish.

The Agricultural Commodity Programs: Two Decades of Experience. Murray R. Benedict and Oscar C. Stine. The Twentieth Century Fund, New York, 1956. Pp. 489. Price $5.00.

The Williams-Waterman Fund. The period 1935 through 1955. Distributed through Research Corporation, 405 Lexington Avenue, New York 17, New York.

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